Draft Guidance for Industry

Professional Flexible Labeling of Antimicrobial Drugs

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

This draft guidance is intended to provide specific guidance on the development of Professional Flexible Labeling (PFL) for therapeutic veterinary prescription antimicrobial drugs.

Draft released for comment on January 22, 1998.

Comments and suggestions regarding this draft document should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, MD 20857. All comments should be identified with Docket Number 98D-0016 and submitted by April 22, 1998.

For questions regarding this draft document, contact John D. Baker, Center for Veterinary Medicine (HFV-110), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-0130 (e-mail: *jbaker@bangate.fda.gov*).

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
January 1998

FOREWORD

The general concepts of **Professional Flexible Labeling** (PFL) may not be equally applicable to all classes of therapeutic prescription products (e.g., antimicrobials, antiparasitics, physiologics). Therefore, CVM intends to develop PFL guidances that are specific to the various classes of drugs. This guidance document specifically addresses the application of PFL concepts to prescription therapeutic antimicrobial products.

The PFL concept has been a topic of discussion for many years. More recently, workshops on PFL were held in April and December, 1995. These workshops were co-sponsored by the Food and Drug Administration/Center for Veterinary Medicine, the American Academy of Veterinary Pharmacology and Therapeutics, the Animal Health Institute, and the American Veterinary Medical Association. A summary of the discussions and opinions expressed in the April, 1995 workshop were published in the Journal of the American Veterinary Medical Association (JAVMA), October 1, 1995. At the conclusion of the December, 1995 workshop, a task force was assembled to prepare a report on PFL concepts. The task force report, which included a model drug label, was published in the JAVMA, July 1, 1996.

The basic concept of PFL is to provide prescription veterinary products that carry useful prescribing information for the range of clinical situations included within their approved conditions of use. Implementation of PFL is based on the recognition that veterinarians, as a function of their medical training, possess the knowledge, skills, and abilities to interpret diagnostic and prescribing medical information and can develop these data into appropriate therapeutic regimens. Ultimately, products labeled as described in the PFL guidance will be consistent with, and better reflect how veterinary medical professionals utilize animal drugs in the course of their professional practice.

A sponsor may follow the guidance provided in this document, or a sponsor may choose to follow alternate procedures or practices. If a sponsor elects to use alternate procedures or practices, that sponsor may wish to discuss the matter a priori with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable to FDA. Although this guidance document does not bind the agency or the public, it represents FDA's current thinking on the development and labeling of therapeutic veterinary prescription antimicrobial drugs. When a guidance document states that a requirement is imposed by statute or regulation, that requirement is legally binding, and its force and effect are not changed in any way by virtue of its inclusion in this guidance.

FDA may amend this guidance document based upon comments submitted by interested persons. Submit written comments on the guidance document to the Dockets Management Branch (HFA-305), U.S. Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

Additional or updated copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855, telephone (301) 594-1755.

INTRODUCTION

In the past, CVM has approved veterinary prescription antimicrobial products that are labeled with single fixed dosages for a narrow range of specific diseases and organisms. Such restricted labeling has led to veterinary prescription products that have limited practical usefulness if administered strictly according to their approved conditions of use. The very narrow label indications often failed to address the fact that, while some specific bacteria produce repeatable, recognized disease, many organisms are either opportunistic or are known to produce a variety of clinical manifestations. In addition, with the approval of single fixed dosages, the efficacy of some products could become suboptimal as bacterial susceptibility patterns change with time.

Veterinarians, in the course of their professional curriculum, are trained in microbiology, the interpretation of bacterial culture and sensitivity determinative procedures, and pharmacokinetics. This knowledge provides licensed practitioners the ability to determine the appropriateness of a particular antibiotic for a specific case. The intent of this document is to describe how the PFL concepts can be applied to prescription antimicrobial products to enable veterinary practitioners to apply their expertise to appropriately, effectively, and safely use antimicrobials for specific clinical cases. The following discussion provides specific guidance on the development of PFL labeling for therapeutic veterinary prescription antimicrobial drugs.

PRESCRIPTION STATUS

Under section 502 (f)(1) of the Act, a drug is deemed to be misbranded unless its labeling bears adequate directions for use. Title 21, part 201, section 105 of the Code of Federal Regulations (CFR) exempts drugs from section 502 (f)(1) of the Act if the drug is in the possession of a licensed veterinarian for use in the course of professional practice, is dispensed in accordance with section 503(f) of the Act, and its label bears certain stipulated information. Likewise, section 504 of the Act stipulates that a veterinary feed directive drug, a drug intended for use in or on animal feed which is limited to use under the supervision of a licensed veterinarian, is exempt from section 502(f) when labeled, distributed, held, and used in accordance with the conditions setforth in section 504.

Drugs labeled in accordance with the concepts of professional flexible labeling require the training of licensed veterinarians to help ensure appropriate clinical usage. Such labels would not provide adequate directions for use by the lay person. Therefore, the use of PFL on veterinary drugs which are not prescription or veterinary feed directive drugs would cause them to be misbranded under section 502 (f)(1) of the Act. Accordingly, the PFL concepts discussed in this document may apply to either veterinary prescription or veterinary feed directive antimicrobial drugs.

INDICATIONS

An indication or indications are required on the label. There is latitude on how an indication can be described on a label. One objective of PFL is to generate labels which are more consistent with the data base supporting the product's approval. The degree of specificity of the indication depends on the characteristics of the drug, the data base supporting the approval, and the nature of the disease(s) for which there is clinical confirmation of effectiveness. If the data base supporting the drug is sufficiently broad, a more general indication is possible; conversely, a more specific indication is necessitated with a more limited data base. These aspects are explained in the remainder of this section.

The following recommendations are provided regarding the INDICATIONS section of PFL-labeled products:

1. The product indication should stipulate the specific animal species for which the product is approved.

   More specificity may be needed and may appear elsewhere on the label when the drug is intended to exclude certain classes in that animal species, e.g., where a product should not be used in lactating dairy cattle or when the drug should not be used in young animals.

2. With an appropriate data base, the INDICATIONS section of the product label can describe the intended use of the product in more general terms that do not stipulate a specific disease condition(s) and/or associated microorganism(s). If the indication is written in this manner, it must be immediately followed by information regarding the specific disease condition(s) for which the drug was shown to be clinically effective. This information provides the basis for approval of the broadly stated indication, but does not limit the use of the product to the described disease conditions that were clinically evaluated.

   EXAMPLE:

   INDICATION

   SUPERMYCIN is indicated for the management of diseases in cattle associated with bacteria susceptible to exoxysporin sulfate.

   EFFICACY CONFIRMATION

   SUPERMYCIN has been shown to be clinically effective under field conditions for the treatment of bovine respiratory disease associated with *Pasteurella haemolytica* and *Pasteurella multocida*.

Criteria that must be met for a broadly stated indication:

A drug sponsor must provide substantial evidence which demonstrates that the proposed product is safe and effective for the management of a specific disease associated with specific bacteria in a specific animal species.

For a broadly stated indication to be acceptable, the sponsor also must provide substantial evidence to support an extrapolation of drug efficacy to the management of the general class of diseases. Substantial evidence for a broad-based claim, should include, but may not be limited to the following:

1. It must be shown by pharmacokinetic (PK) data or other means (e.g., tissue concentrations) that the active drug is systemically available and can distribute to peripheral sites where infections, other than those studied clinically, would occur. Products which act locally should only be indicated for the management of diseases for which such locally acting products may be effective. Drugs which inherently have limited distribution and/or that concentrate in specific tissues/organs (e.g. urinary bladder) cannot claim effectiveness for diseases which are known to occur at locations where the drug cannot reasonably be expected to reach therapeutic concentrations.

2. The product must be labeled with a dosage or dosage range that can reasonably be expected to produce therapeutic drug levels at the sites of disease occurrence. It would be inappropriate to label an antimicrobial product for a broad-based claim if the drug is not likely to attain drug concentrations necessary to be effective against pathogens other than those tested clinically.

3. There should also be a demonstration that pathogens associated with other target animal diseases are susceptible to the drug. Therefore, susceptibility data are needed for pathogens other than those involved in clinical confirmation trials. Potentially, these other pathogens should be susceptible to achievable blood or tissue levels of the active moiety. (Other features regarding microbiological information on the label are given below.)

Alternatively, the conditions for a broadly stated indication could be met by demonstrating clinical effectiveness for treatment of a variety of clinical diseases. The diseases should involve a variety of different pathogens, and they should affect a variety of different body sites. The pathogens and body sites should be sufficiently different to support the substantial evidence described above to show that the drug is effective to manage the general class of diseases.

We acknowledge that a broad-based indication may not be feasible or appropriate in certain situations. It is presented as one method of expanding drug utility in the context of PFL. We note that it is acceptable to have a more specific indication, and a more specific indication is required when the substantial evidence does not exist to support a broadly stated indication.

DOSAGE AND ADMINISTRATION

The Dosage and Administration section of the label is required. This section should include drug administration information (e.g., route) and a complete description of the dosage or dosage range including dose amount(s), interval(s), and duration(s) for each indication when appropriate. This section should also state any modification of dosage needed in specific patient populations, (e.g., in patients with renal disease, etc.) and, if applicable, the use of loading doses. Specific tables may be provided to describe dosage schedules and could include such information as animal species, indication, route of administration, and any specific directions for preparation of the dose such as reconstitution and dilution. There is also latitude on the inclusion of information pertaining to repeat treatment.

A label may contain either a single point dosage or a dosage range for a particular indication or animal species. Any element of the dosage can be variable and selection of a point dosage or dosage range depends on the database and disease condition. Justification must be given to support the upper and lower ends of the dosage range. Products intended for use in food-producing species of animals must have a withdrawal time established for the highest approved dose for the longest approved duration of treatment.

The sponsor must provide substantial evidence that the lowest approved dosage in the dosage range is effective. It is not necessary to determine the minimally effective dose. The high end of the dosage range can be established by a number of factors, such as target animal safety, human food safety issues related to drug withdrawal times in food animals, and practical considerations of quantity of drug that needs to be administered to achieve a certain dose. The factor that was used to establish the upper dosage limit should be indicated on the label if it involves something other than practical considerations of limitation on quantity to be administered (e.g., target animal safety, or drug withdrawal time).

Drug sponsors are encouraged to provide guidance regarding therapeutic dosage adjustment. This could be a simple statement of principles to use for dosage adjustment (e.g., change the dosage based on the results of susceptibility testing). Alternatively, more complex principles could be provided in product labeling.

MICROBIOLOGY

The MICROBIOLOGY section of the label is not required for product approval. However, certain aspects regarding susceptibility of target animal pathogens should be included in the MICROBIOLOGY section of the label to support a broadly stated indication.

The objective of the following discussion is to provide the framework for developing a MICROBIOLOGY section that is consistent with other aspects of labeling and is useful to veterinary practitioners for making therapeutic decisions (e.g., by describing the drug's spectrum of activity or by providing guidance for selecting an appropriate dosage). The intent of this discussion is *not* to define a fixed format for presenting susceptibility data.

CVM believes that the MICROBIOLOGY section should at a minimum provide information on the spectrum of activity of the drug. This information assists the veterinarian in making a decision as to which drug to consider for treating a particular clinical case. The drug's spectrum of activity can be characterized by providing information regarding the susceptibility of various microorganisms isolated from animals. This susceptibility information may include isolates obtained from animals in field trials in which the clinical effectiveness of the drug was evaluated, but may also include susceptibility information regarding microbial isolates that have been collected from other sources such as diagnostic laboratories. The collection and presentation of such susceptibility information is discussed in more detail later in this section.

In addition to characterizing the drug's spectrum of activity, information in the MICROBIOLOGY section can assist in making decisions regarding the selection of an appropriate treatment regimen for a specific case. This is of particular importance for dosage-ranged products in which immediate decisions may need to be made regarding dose amount, duration, or interval.

It is important to note that the MICROBIOLOGY section is not intended to be the primary source of information on contemporary susceptibility of pathogens associated with particular cases being treated. The *in vitro* data contained in the MICROBIOLOGY section should provide the veterinary practitioner with additional information which can be used with other aspects of his/her professional training to manage disease.

The *in vitro* data alone do not imply any claim of clinical effectiveness, nor does it describe the basis or scope of a broad indication. To accurately characterize the *in vitro* data provided, it is important that the label clearly note which organisms were obtained from clinical trials, which were obtained from microbiological surveys, and whether such *in vitro* susceptibility information has been determined to correlate to clinical response.

Those organisms listed in labeling that were obtained from clinical trials were isolated in association with the specific disease condition(s) under which the clinical efficacy of the product was confirmed. However, unless the *in vitro* susceptibility data (MIC values) presented for such organisms represent established breakpoints, it should be noted that the correlation between such susceptibility data and clinical response has not been determined.

Those organisms listed in labeling that were obtained from sources other than clinical trials (e.g., a survey of isolates from diagnostic laboratories) should be clearly identified as such. In addition, it should be noted that the correlation between the *in vitro* susceptibility data (MIC values) presented for such organisms and clinical response has not been determined.

PRESENTATION OF SUSCEPTIBILITY DATA:

CVM recognizes that susceptibility data are highly variable and dependent on numerous factors including the characteristics of the survey conducted to collect the clinical isolates. Additionally, the potential for susceptibility patterns to change with time limits the utility of susceptibility data and necessitates that it be periodically updated.

We believe that the current standard of veterinary care includes appropriate culturing and susceptibility testing to determine pathogen susceptibility for specific cases. We also acknowledge that in many cases it is not practical to obtain such information, or that therapeutic decisions must be made before such information can be obtained. Therefore, although we acknowledge that product labels cannot and should not be the primary source for contemporary susceptibility information, we also acknowledge the practical need to provide adequate information to make immediate therapeutic decisions, particularly for dosage-ranged products.

Two alternative approaches for presenting susceptibility information are provided as examples below. The approach selected is dependent on the quality and quantity of the available database. The first approach stipulates that specific susceptibility information be provided for individual pathogens realizing that such susceptibility information is likely to change with time. Drug sponsors should be committed to updating susceptibility information after the product is originally approved. The second approach stipulates that susceptibility information be provided for all pathogens listed on labeling as a single inhibitory concentration. Although this approach provides information which is less time sensitive, it requires that practitioners seek other sources to obtain susceptibility information for individual pathogens.

Microorganism-specific susceptibility data:

The intent of providing pathogen-specific susceptibility information on labels is not to obviate the need for culture and susceptibility testing for individual cases. Rather, it is to provide the practitioner with information regarding the spectrum of activity of the drug, the relative susceptibility of various pathogens, and to provide some basis upon which immediate therapeutic decisions can be made.

Pathogen-specific susceptibility information that is collected for inclusion in labeling is often the result of limited *in vitro* susceptibility surveys, and may not reflect the susceptibility of the pathogen(s) associated with a particular case. Although such information may be useful as a guide, it must be interpreted with caution and with an understanding of the limitations of its applicability. Therefore, it is important that such data be presented in a manner which adequately characterizes its derivation and its clinical significance.

The following points should be considered when presenting pathogen-specific susceptibility information on product labeling.

1. The susceptibility information for individual pathogens should be presented as minimum inhibitory concentrations (MICs). Furthermore, this information should be presented in a manner which describes the distribution of MICs in the sample surveyed. For example, the label could present the concentration at which 50% and 90% of the sample isolates were susceptible (MIC_{50} and MIC_{90}), or it could present, in tabular format, the distribution of the sample isolates relative to the inhibitory drug concentration. Presenting *only* an MIC range for each pathogen surveyed is not recommended because it does not provide information regarding the actual distribution of MIC values for individual isolates within the range.

2. When available, criteria (e.g., established breakpoints) for interpreting the susceptibility information should be provided in the MICROBIOLOGY section.

3. As discussed under a subsequent section of this document entitled *Limitations,* microorganism

susceptibility patterns are likely to change over time. This is of particular concern when specific susceptibility information is provided for individual pathogens. Therefore, the susceptibility information in the MICROBIOLOGY section of the label should indicate the date of sample collection.

4. If susceptibility information for individual pathogens is presented, drug sponsors should periodically update product labeling with contemporary susceptibility information.

5. The MICROBIOLOGY section of the label should contain a recommendation that culture and susceptibility testing be done to determine the susceptibility of the pathogen(s) associated with specific cases.

6. The susceptibility information should be presented in a format which, in conjunction with other label information, may facilitate decisions regarding the selection of appropriate dosages for particular cases.

Single inhibitory concentration:

In an effort to address the limitations of providing microorganism-specific susceptibility data on product labeling (e.g., time-sensitivity, relevance to specific clinical cases), an alternative approach to presenting susceptibility information could be considered. This alternative approach places more emphasis on describing the spectrum of activity of the drug rather than on specifically describing the susceptibility of individual pathogens to the drug.

This approach would provide a single reference drug concentration at which 90% of the isolates for all listed microorganisms were found to be susceptible. No microorganism-specific susceptibility data would be provided. Therefore, in order for a given pathogen to be included on the list of label microorganisms, 90% of the isolates tested for that pathogen must be found to be susceptible when exposed to a given concentration of the drug under *in vitro* conditions. The product user would be able to identify whether a pathogen of interest was included in this list of susceptible organisms, but would not be provided with susceptibility information regarding that specific pathogen. Microorganism-specific susceptibility data would have to be obtained from sources other than the product label.

The following points should be considered when susceptibility information is presented relative to a single drug concentration.

1. A single reference drug concentration is provided at which 90% of the isolates for all listed microorganisms were found to be susceptible. The single reference concentration would refer to all microorganisms listed on the label. No microorganism-specific susceptibility data would be provided.

2. The reference concentration should be clinically relevant; one that is readily achievable in the blood or appropriate local target organ. It should not necessarily be the peak concentration, but rather it should be a concentration that is sustainable for a clinically relevant period of time.

3. The reference concentration can be estimated from what is known about the pharmacokinetics, pharmacodynamics, and inhibitory concentrations of the drug, and the relationship between clinical response and inhibitory concentrations.

4. The list of microorganisms included is intended to provide information on the general spectrum of activity of the drug. It is intended to be used in conjunction with diagnostic culture and susceptibility results pertaining to the case(s) being treated at the time of use. The label should contain a recommendation that culturing and susceptibility testing be done.

5. The susceptibility information should be presented in a format which, in conjunction with other label information, may facilitate therapeutic decisions regarding the selection of appropriate dosages for particular cases. Since immediate therapeutic decisions often need to be made prior to obtaining culture and susceptibility results, the label should provide enough information to support such decisions (e.g., the label might state that the reference concentration is likely to be attained when a dosage of X mg/kg is administered).

COLLECTION OF IN VITRO SUSCEPTIBILITY DATA:

Source of isolates:

1. The microorganisms identified in the MICROBIOLOGY section of the label should be potential pathogens associated with the target animal species.

2. In most cases, the *in vitro* susceptibility data should be derived from clinical isolates obtained in the U.S. from the target animal species.

3. The microbiological susceptibility information may include data derived from clinical specimens obtained from foreign sources. It is the responsibility of the sponsor to demonstrate that the foreign data are microbiologically relevant to use of the product in the U.S.

Number of isolates:

The minimum number of isolates required for a given pathogen is dependent on the recognized prevalence of that pathogen in the animal population. For prevalent pathogens found in multiple animal species, a substantial number of isolates should be tested. For pathogens that are not prevalent in the animal population, are found in limited animal species, and/or are fastidious, testing of fewer isolates may be acceptable. The sponsor should consult with CVM regarding the specific requirements regarding the number of isolates needed.

Methodology:

The testing of clinical isolates should be done using a method generally recognized by scientific experts as acceptable for susceptibility testing. The testing process should include appropriate quality controls.

PROMOTIONAL CONSIDERATIONS:

Promotional materials dedicated only to *in vitro* data, without equivalent demonstration of clinical effectiveness of the given antimicrobial drug product, would be deemed by the FDA, under most circumstances, to be misleading.

LIMITATIONS:

All *in vitro* susceptibility information provided for organisms listed in product labeling should be clearly identified as to the general source of the isolates (i.e., from clinical trials or from microbiological surveys). In addition, a statement such as the following should accompany *in vitro* susceptibility data listed in labeling if its correlation to clinical response has not been determined:

"The correlation between *in vitro* susceptibility data (MIC values) and clinical response has not been determined."

1. If data exist that cast doubt on the potential clinical effectiveness of the antimicrobial product to treat infections associated with a listed microorganism(s) at a particular body site, the *in vitro* data for such microorganisms should be footnoted to provide such information.

2. For products indicated for use in food animal species, the MICROBIOLOGY section should *not* provide microbiological susceptibility information for pathogens, which if treated, would require the product be used in a manner for which adequate food safety information is not available. For example, it would be inappropriate to include an obligate mammary gland pathogen in the MICROBIOLOGY section of a product which is only approved for parenteral use in nonlactating cattle. Treatment of such a pathogen would necessitate that the product be used in a manner for which there is no human food safety information.

3. Due to changing microorganism susceptibility patterns, the microbiological susceptibility information should be derived from contemporary clinical isolates. The dates during which the isolates were obtained should be noted in the MICROBIOLOGY section.

DRUG WITHDRAWAL TIME(S)

When a product is labeled with a single point dose, a residue depletion study must be conducted at this dose for the maximum duration of therapy. However, when a product is labeled with a dosage range, there are a number of alternative approaches for developing withdrawal time information. The various options are described in general terms below. Drug sponsors should discuss the various options with CVM to determine the approach that is most appropriate for the product in question. In addition, all applicable toxicology studies as well as total residue and metabolism studies would be required.

1. The withdrawal time would be established using a traditional residue depletion study at the highest labeled dosage. Although approved with a dosage range, only one withdrawal period would appear on the label. Therefore, a statement warning against withdrawal time interpolation in lower dosages should appear on the product label.

2. The withdrawal time would be established using a traditional residue depletion study at the highest labeled dosage and at any lower dosages/indications for which the sponsor wanted a shorter withdrawal period. Each withdrawal period would appear on the label in a stairstep fashion and would be applicable for all dosages at or below the dosage for which the withdrawal period was established.

This approach may be particularly useful where the depletion profile indicates that the range of proposed dosages results in nonlinear kinetics. The sponsor could establish a withdrawal time for the highest dosage and at any lower dosages for which a shorter withdrawal period was desired. This might be applicable to those products where a wide dosage range was desired and where the high dosage withdrawal period would not be desirable and/or appropriate as the sole labeled withdrawal period. This approach would require multiple residue depletion studies.

3. The withdrawal time would be established using a traditional residue depletion study at the highest labeled dosage. Lower dosage levels (*i.e.*, 50%, 25%, 12.5%, *etc.*) would have withdrawal times assigned by subtracting one tissue half-life from the withdrawal time determined in the residue depletion study. These withdrawal periods would appear on the label in a stairstep fashion and would be used for all dosages at or below the dosage for which the withdrawal period was applicable.

   This approach would require that only one residue depletion study be conducted at the highest label dosage and that applicable withdrawal times for lower dosage levels be mathematically calculated. The sponsor would have to demonstrate nonsaturable absorption and drug distribution about the dosage range. This approach would probably be applicable to only those products where a wide dosage range was desired and tissue half-lives were long.

4. A special approach could be considered for drugs requiring a withdrawal period at higher doses and qualifying for a zero withdrawal at some lower dose. The zero withdrawal would appear on the label with its applicable dose. A withdrawal period also would appear on the label for the highest dose. Additional withdrawal times would appear on the label in a stairstep fashion either as the result of individual tissue residue depletion studies (where each withdrawal time would be applicable for all doses at or below the dose for which the withdrawal period was established, as in #2 above) or, where tissue residue depletion was linear across the dose range, by subtracting one tissue half-life from the withdrawal time determined in the residue depletion study for each incremental decrease in dose (as in #3 above).

   The sponsor would conduct a single-point cold residue study at zero withdrawal for the dose that supported the zero withdrawal and at least one traditional residue depletion study, conducted at the highest labeled dose, to establish the withdrawal times for all dosages higher than the zero withdrawal dosage. If additional intermediate withdrawal times were desired, they could be established by #2 or #3 above, as applicable. It would not be acceptable to interpolate to a zero withdrawal.

PHARMACOKINETICS/PHARMACODYNAMICS

Drug sponsors often collect pharmacokinetic (PK) data during drug development. These data are useful for many purposes, particularly as an aid in determining a dosage. Sponsors are encouraged to include target animal PK information on the product label which supports the therapeutic decision making process. However, they should obtain CVM comments regarding their specific plans before collecting the data.

Despite the many clinical applications of PK data, it may not be used as a substitute for the clinical

demonstration of product efficacy (demonstration of product bioequivalence is an exception). However, PK data can be used to meet one of the criteria for a broadly stated indication, as described above. If this is the case, appropriate PK information must be included on the product label.

TOXICOLOGY, TARGET ANIMAL SAFETY AND EFFICACY

It has been acceptable to provide summaries of safety and efficacy studies in the target animal on labels, and this policy will continue. In addition, CVM will continue to consider the inclusion of certain non-target animal safety information on labels as appropriate.

LABEL FORMAT

In consideration of the extensive amount of information that could be presented on a label, information should be arranged in a concise and easy to use format. Specifications regarding the *content* of prescription veterinary drug labels are stipulated in 21 CFR 201.105. However, no specific regulations currently exist regarding the *format* (i.e., standard order of label sections, etc.) of labeling for prescription veterinary drugs.

The PFL concept is intended to provide "flexibility" in the labeling of prescription veterinary products. Although CVM supports this spirit of flexibility, there is also a need to retain a level of consistency in the format in which veterinary products are labeled. From a practical standpoint, such consistency is important in that practitioners become familiar with label format and know where to look for certain information. Without some level of label format standardization, labels for similar products could appear quite different leading to confusion when trying to locate needed information. Although this document is not intended to establish the standard for label format, it is intended to serve as working guidance for products to which this PFL document is applicable.

The following label sections are listed in the order in which they are recommended to appear in the package insert. All the label information listed below is not required on labeling for product approval. All information included on product labeling, whether or not required for product approval, is based on data reviewed by the FDA/CVM. The label sections below are listed under general subject headings for the purposes of this document to provide some rationale for the order of section presentation.

Product information:

1. Drug name
2. Prescription status *(i.e., Rx caution statement)*
3. Description *(inclusion of chemical structure is optional)*
4. How supplied
5. Storage conditions

Product use information:

6. Indications
7. Efficacy confirmation *(required for broad-based indication)*
8. Dosage and Administration
9. Contraindications *(if applicable)*

Product use implications for public health and/or animal health (if applicable):

10. Residue Warnings
11. Warnings
12. Adverse Reactions
13. Precautions

Clinical pharmacology information: (certain aspects may be required for broad-based indication)

14. Microbiology
15. Pharmacokinetics

Information regarding product efficacy:

16. Efficacy

Information regarding product safety:

17. Toxicology
18. Target Animal Safety